

### **REMARKS**

The Office Action mailed December 14, 2008 has been carefully considered and the following response prepared. Claims 3-10, 16, 18, 19 and 21-25 are pending in the application. Claims 8, 17 and 22-24 have been canceled without prejudice. Claims 10 and 16 have been amended to recite that the method or formulation is for averting or reducing the risk of postoperative ischemia-reperfusion injury, as discussed below. Claims 10, 16 and 25 have been amended to specify that the precursors of glutamine are in the form of a di- or tripeptide containing glutamine. Support for this amendment can be found throughout the specification and in particular at page 10, lines 13-18 and 26-27. New claim 26, directed to the formulation of claim 16 wherein component b) is glutamine, has been added. Claim 4 has been amended to remove "and/or." Claim 25 has been amended to delete "or a glutamine precursor."

### **Rejection under 35 USC 112, first paragraph (enablement)**

At page 2 of the Office Action, the Examiner maintained the rejection of claims 3-10, 16, 18-19, 21 and 23-25 under 35 USC 112, first paragraph as not enabled. The Examiner stated that the specification, while being enabling for a composition and a method for reducing the risk of postoperative ischemia reperfusion injury, does not reasonably provide enablement for a composition and a method which is effective in reducing the risk of any and all postoperative complications as instantly claimed.

Applicants again traverse this rejection. In order to advance prosecution, claims 10, 16 and 25 have been amended limit the postoperative complications to postoperative ischemia-reperfusion injury. Claims 3-7 and 9 depend from claim 10 and are also amended by the amendment to claim 10. Claims 18, 19, 21 and new claim 26 depend from claim 16 and are also amended by the amendment to claim 16. In view of the foregoing amendments to the claims to limit them to subject matter stated by the Examiner to be enabled, withdrawal of this section 112, first paragraph rejection is respectfully requested.

**Rejection under 35 USC 103**

At page 6 of the Office Action the Examiner maintained the rejection of claims 3-10, 16, 18-19 and 21-25 under 35 USC 103 as obvious over Inanami et al. (Free Radic Res), Schneider et al (U.S. Patent 6,656,608), Sherrat et al (U.S. Patent 6,423,359) and Schneider et al. (U.S. Patent 5,902,829). In the present Office Action, the Examiner commented on the declaration by Dr. Schneider submitted on September 19, 2007 in support of the patentability of the claims. The Examiner indicated that Applicant's invention is predicated on an unexpected result, but the claims are not commensurate in scope with the particular conditions which would lead to an unexpected result as disclosed in the declaration.

Applicant again traverses this rejection. Claims 10 and 16 have been amended to recite a composition comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof. Claims 3-7 and 9 depend from claim 10 and are also amended by the amendment to claim 10. Claims 18, 19, 21 and new claim 26 depend from claim 16 and are also amended by the amendment to claim 16. In independent claim 25 as amended, the composition comprises green tea extract and glutamine.

Inanami et al. discloses oral administration of (-)catechin from green tea to gerbils for two weeks prior to surgery wherein the surgery induced transient focal brain ischemia. Administration of (-) catechin continued one week after surgery. The authors found that oral administration of (-) catechin protected the animals against ischemia-reperfusion-induced neuronal death.

Schneider et al. (U.S. Patent 5,656,608) disclose the use of one or more of the amino acids glycine, alanine and serine in combination with a) omega-3 polyunsaturated fatty acids; b) arginine or ornithine or pharmaceutically acceptable salt of arginine or ornithine; or c) RNA, nucleotide or nucleoside; or mixtures of one or more of a), b) and c) to prevent or minimize the effects of hypoxia-reperfusion injury. When used to minimize the effects of ischemia-reperfusion injury, column 7, lines 9-13 disclose that a dietary supplement containing the

foregoing can be administered over a period of three days or longer before surgery, generally three to six days before surgery. Such supplements are disclosed at column 6, lines 21-61 as comprised of energy sources in an amount supplying from 600 to 1,000 Kcal/day. Schneider et al. does not disclose or suggest administration of green tea extract for any purpose, much less to prevent or reduce postoperative complications.

Sherratt et al. discloses compositions comprising glutamine in combination with other nutrients, including N-acetyl-cysteine and Vitamins A, C, E that can be administered for promoting recovery in patients undergoing elective surgery and for treating multiple organ system failure. The compositions are administered to patients before and after elective surgical procedures, in particular 1-2 days prior to and/or after elective surgical procedures

Schneider ('829 patent) discloses the use of L-arginine, a precursor of L-arginine and/or physiologically acceptable salts thereof, or (i) a nitric oxide donor, and/or (ii) a substrate of the nitric oxide synthetase, and/or (iii) a precursor of the said substrate, in the preparation of a medicament or nutritional formulation for the amelioration of micro-circulatory hypo-perfusion, and/or the treatment or prophylaxis of hypoperfusion-reperfusion injury, in patients which have undergone elective surgery, characterized in that the medicament or nutritional formulation is pre-operatively administered to the patient. Schneider et al. ('829 patent) discloses glutamine as a precursor of L-arginine. Schneider et al. ('829 patent) further discloses that the medicament is administered at least one day prior to surgery, but can be initiated between 3-10 days prior to surgery.

The claimed compositions and methods are not obvious on view of Inanami et al. (Free Radic Res), Schneider et al (U.S. Patent 6,656,608), Sherratt et al (U.S. Patent 6,423,359) and Schneider et al. (U.S. Patent 5,902,829). None of the cited references, alone or in any combination, disclose or suggest the methods of amended claims 3-10, 16, 18-19 and 21-25 and new claim 26 of averting or reducing the risk of postoperative ischemia-reperfusion injury, wherein a composition comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or

combinations thereof, is gastrointestinally administered to a surgical patient less than twenty-four hours before a surgical procedure.

Applicants have surprisingly found that administration of the claimed composition to a surgical patient less than 24 hours before a surgical procedure averts or reduces the risk of postoperative complications. The Declaration of the inventor Dr. Heinz Schneider, previously submitted, presented experimental data showing that green tea extract together with glutamine ameliorates ischemia-perfusion injury, whereas a solution of glutamine in combination with other antioxidants did not provide protection against postoperative complications.

Claims 10 and 16 have been amended to recite that component b) of the composition can be a precursor of glutamine in the form of a di- or tripeptide containing glutamine. Applicant submits that compositions containing a precursor of glutamine in the form of a di- or tripeptide containing glutamine would perform in the same manner as compositions containing glutamine. Di- and tripeptides containing glutamine are known in the art to be a source of glutamine in parenteral nutrition.

Applicant submits herewith copies of Fürst et al., Journal of Parenteral and Enteral Nutrition, vol. 14, pages 118S-124S, 1990 (Exhibit A) and European Patent EP 0 087 750 (Exhibit B), which disclose the use of glutamine-containing di- and tripeptides, respectively, as sources of glutamine in parenteral nutrition. Applicant is not aware of an English language equivalent of EP 0 087 750. A translation of two relevant portions of EP 0 087 750 is provided as follows. On page 4, lines 13-14, it is stated: "The use of di- and tripeptides comprising glutamine according to the invention as a source of glutamine is shown in the following examples." Page 2, lines 31-33 state: "After infusion these di- or tripeptides are split in the organism by aminopeptidases being present in the body, for example by peptidhydrolases being present in mammalian tissue, this releasing slowly the glutamine for direct utilization for the production of body proteins." See also claim 1 on page 8.

Thus, Applicant submits that compositions comprising a) green tea extract and b) precursors of glutamine in the form of di- or tripeptides containing glutamine would also be effective to avert or reduce the risk of postoperative ischemia-reperfusion injury when administered with green tea extract to a surgical patient less than 24 hours before a surgical procedure.

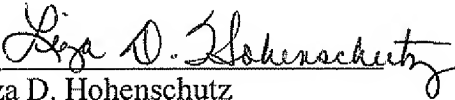
In summary, the compositions and methods of claims 3-7, 9-10, 16, 18-19, 21 and 25, as presently amended, and new claim 26 are not obvious in view of the combined teachings of Inanami et al. (Free Radic Res), Schneider et al (U.S. Patent 6,656,608), Sherrat et al (U.S. Patent 6,423,359) and Schneider et al. (U.S. Patent 5,902,829). Withdrawal of this section 103 rejection is again respectfully requested.

In view of the above, the present application is believed to be in a condition ready for allowance. Entry of the amendments to the claims is requested. The amendments are not believed to present any additional issues, and place the claims in condition for allowance or at least better form for appeal. Reconsideration of the application is respectfully requested and an early Notice of Allowance is earnestly solicited.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 03-2775, under Order No. 09600-00031-US. A duplicate copy of this paper is enclosed.

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Respectfully submitted,

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**EXHIBIT A**

(Fürst et al., Journal of Parenteral and Enteral Nutrition, vol. 14, pages 118S-124S, 1990)

**EXHIBIT B**

(EP 0 087 750)